

Conference on ENTERprise Information Systems / International Conference on Project
MANagement / Conference on Health and Social Care Information Systems and Technologies,
CENTERIS / ProjMAN / HCist 2015 October 7-9, 2015

Abbreviations and symbols in a large sample of medicinal package leaflets: automatic detection and comprehension assessment

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Abstract

Medicines package leaflets (PL) need to be clear and comprehensible, according to legal recommendations. Abbreviations and symbols (A&S) are not recommended since their use may lead to misunderstandings and medication errors. Objectives: 1) identify, typify and quantify all A&S in a large sample of Portuguese PL, 2) detect discrepancies between these A&S and regulations, and 3) assess how educated individuals interpret A&S found in Portuguese PL. Methods: descriptive and exploratory study. Descriptive study - 531 PL were visually inspected in order to identify all A&S and a computer tool was programmed to count these A&S. All A&S were typified according to classificatory groups (e.g. abbreviations of diseases names) and evaluated according to the regulations. Exploratory study - the interpretation of 373 A&S by 26 undergraduates was assessed with a questionnaire. Results: 828 different A&S were identified (6407 occurrences). The average number of A&S per PL was 12.1 (SD=13.1). Thirteen classificatory groups were built. Non-compliant A&S were found. Only a very low percentage of responses was correct (9.9%). Conclusion: A&S were prevalent in PL, contrary to the international recommendations. A significant number of technical A&S was unfamiliar to a group of educated people. Automatic tools and procedures regarding these readability features should be developed in order to validate PL's compliance with regulations.

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Peer-review under responsibility of SciKA - Association for Promotion and Dissemination of Scientific Knowledge

Keywords: Package Leaflets; Readability; Medicinal Products; Abbreviations; Patient Safety

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1. Introduction

In the European Union, all medicines must be accompanied by a package leaflet (PL).¹ PL must contain information on 1) What X is and what it is used for, 2) What you need to know before you <take> <use> X, 3) How to <take> <use> X, 4) Possible side effects, 5) How to store X, and 6) Contents of the pack and other information (X = the name of the medicine),² and must be clear and legible to ensure patients' comprehension.³ PL are usually consulted by patients, potential users of medicines and health professionals.^{4,5} It is well established that the patients with a low literacy level have more difficulty in understanding health information.⁶⁻⁸

In Europe, the PL are developed by the marketing authorization holders and approved by the national medicine agencies of each European country or in some cases by the European Medicine Agency (EMA).¹⁻³ According to the requirements of the EMA, abbreviations, should not in general be used in medicinal PL. Similarly, scientific symbols should be avoided, due to the risk of misinterpretations (e.g. ">" mistaken for "<").^{3,9} Many studies report that the use of abbreviations in PL is unsuitable for the users' comprehension.^{10,11,12} The following abbreviations (A) and/or symbols (S) (A&S) are among those explicitly recommended not to be used: μg (or micrograms: risk of misinterpretation as mg), *U* (or units: risk of misinterpretation as zero or four), numerical dose and unit of measure running together (e.g. *10mL*: risk of misinterpretation as *100* or *1000*), and abbreviations of certain active substances (e.g. *AZT*: risk of misinterpretation as zathioprine or aztreonam) - in these cases, the use of *mcg*, *units*, *10mL*, and *zidovudine* is recommended instead, respectively. Fractions should also be avoided (e.g. $\frac{1}{2}$: risk of misinterpretation as 1 or 2).¹³⁻¹⁵

There are convincing reports on medication errors caused by the inadequate use of A&S.^{16,17} For instance, among the 643,151 medication errors reported in the MEDMARX program 2004-2006, 29,974 (4.7%) were related to the inadequate use of A&S by health professionals, which in some cases caused the patient's death.¹⁶ In Portugal, 21,594 cases of intoxication were reported, and 3,085 of these (14.2%) were related to the incorrect use of medicines (2011). The exact number of events resulting from the patients' misinterpretations of A&S is however not known.¹⁸

The aims of this study were:

- To identify, quantify and classify A&S in an extensive sample of package leaflets (Objective 1).
- To detect discrepancies between these A&S and the legal requirements (Objective 2).
- To assess educated peoples' interpretation of a sample of A&S (Objective 3).

This paper is organized as follows. In section 2 we provide the details about the methods followed in the studies conducted, in section 3 we present our major results, in section 4 the results are discussed, and practical implications and limitations are identified. We conclude in section 5 with some final remarks.

2. Methods

A descriptive study was conducted in order to address objectives 1 and 2, and an exploratory study was carried out so as to address objective 3.

2.1 Descriptive study

All names of brand medicines mentioned in the Portuguese Prescribing Guide¹⁹ were collected in a *MS Excel file*. This national guide is developed in collaboration with Infarmed (the Portuguese medicine agency) and describes the majority of the Portuguese medicines. A sample of 531 (28.5%) brand names of medicines was randomly selected from all (100%) the branded names mentioned in this guide.¹⁹ The 531 PL were consulted in *Infomed* (the Portuguese public database with information on medicines).²⁰ The sample size was conveniently defined.²¹ PL of generic medicines were excluded because these are identical or very similar to the PL of branded medicines.¹

Firstly, all A&S were manually identified in each PL, since the scientific A&S present in glossaries of medicinal bibliographic sources^{19,22,23} were not always identical to those used in the PL.

Secondly, these A&S were post-hoc classified as follows:

- Units of measure (e.g. *mg/5mL*) (Group 1);
- Chemical symbols of excipients, package materials, etc. (e.g. *HDPE*: high-density polyethylene) (Group 2);
- Fractions or numbers in association with symbols or letters (e.g. *<1/10*, *8/8 h*) (Group 3);
- Names of diseases (e.g. *ADHD*: attention deficit hyperactivity disorder) (Group 4);
- Microorganisms, such as bacteria or viruses (e.g. *HPV*: human papillomavirus) (Group 5);
- Drug names or therapeutic-related information (e.g. *ZDV*: zidovudine) (Group 6);
- Information on drug administration (e.g. *i.v.*: intravenous) (Group 7);
- Information on anatomical and/or physiological issues (e.g. *LDL*: low-density lipoprotein) (Group 8);
- Enzymes (e.g. *G6DP*: glucose-6-phosphate dehydrogenase) (Group 9);
- Mathematical or pharmacokinetic symbols (e.g. "+", *AUC*: area under the curve) (Group 10);
- Marks on the surfaces of medicines (e.g. logotypes) (Group 11);
- Items of common use (e.g. "®" for trademark or *CE* for European products) (Group 12);
- Other A&S not related to any of the above categories (e.g. *EMA* for European Medicine Agency) (Group 13).

Two pharmacists coded the A&S through a consensus process. The codifications were based on reliable bibliographic sources.^{19,22,23} Furthermore, the A&S with full correspondence in a language other than Portuguese, such as English or Latin were quantified (e.g. *NSAID*: non-steroidal anti-inflammatory drugs instead of *AINE*: *anti-inflamatório não esteróide*).

Thirdly, a software application (PreText) was programmed to automatically identify and count the A&S.²⁴ The reliability of the tool was checked during the PL analysis, and at the end of the process 20 PL (3.7%) were randomized to be double-checked. No errors were detected.

The medicines of the sampled PL were classified as follows: 1) prescription-only or over-the-counter (OTC) medicines, 2) medicines approved via a centralized (or *a single marketing authorization that is valid in all EU countries*) or non-centralized procedures (all the other types of approval procedures),²⁵ 3) medicines with different routes of administration, and 4) medicines from different therapeutic groups, in accordance to the data available in *Infomed*.²⁰ These 4 classificatory groups were selected because: 1) OTC medicines may be freely acquired without the intervention of a health professional,^{1,10} and thus the clarity of the information of the PL of OTC medicines is especially relevant, 2) PL of medicines approved via a centralized procedure²⁵ are available in all European countries, and therefore our study may be of particular relevance in this group, given the potential for generalization of our results and/or procedures to PL existing in other European countries, and 3) some routes and therapeutic groups may be more hazard than others (e.g. dermatologic vs. parenteral medicines).²⁶

2.2 Exploratory interpretation study

An exploratory study to assess participants' interpretation of a set of medicinal A&S was conducted using a questionnaire. All selected participants were university undergraduates from non-biomedical studies.

2.2.1 Questionnaire development

A questionnaire was built to collect participants' socio-demographic data and interpretation on the sampled A&S. Firstly, a total of 525 A&S were conveniently identified in 3 glossaries of standard medical literature,^{19,22,23} and secondly, in order to limit the size of the questionnaire, a random sample of 373 A&S (ca. 70%) was selected. 362 of the 373 A&S (97%) were classified as abbreviations and 11 (3%) as symbols. Each of these A&S was browsed in a public database of current Portuguese texts (extracted, for instance, from newspapers), containing more than 221 million words in order to check if they were familiar/frequent in the current language.²⁷ According to the results of this study: 29 A&S (10.4%) occurred once in one million words and the remaining A&S were not found in the database. This confirms the A&S under evaluation have a low frequency in the language, if they exist at all, and tend in general not to be used in non-technical texts.

The questionnaire used a tabular format: 1) the A&S (e.g. *MAO*) were presented in the first column, 2) the correspondent full meaning of each A&S (e.g. monoamine oxidase inhibitor) was presented in the second column, 3) participants were instructed to signal in the third column whether they knew the meaning of the A&S ("yes" or "no"), and 4) if the answer was "yes", they were asked to give a brief description of the meaning of the A&S in the fourth column. Null answers and wrong explanations were classified as incorrect and all the others as correct. Two specialist independently re-checked the correct answers. The fulfillment of questionnaire by the participants was not time limited, and all the participants fulfilled the questionnaire in less than 1 h.

The questionnaire comprised 23 control questions (one per page) to check participants' attention. The control items were selected from common A&S available in the PL (e.g. *Fig.* or *figure*). The familiarity/frequency of the control A&S was checked in the same public database of current Portuguese (10 control A&S with 1 to 10 occurrence per million, and 13 control A&S with 10 or more occurrences per million).²⁷ The tested and control A&S were alphabetical ordered. The questionnaire was divided into two approximately equal parts (186/187 questions plus 11/12 controls per questionnaire) and administered in two classes of undergraduates during the same week. Written instructions were given in the first page of questionnaire and any remaining questions were answered by the researcher. All data were anonymous and confidential.

2.2.2 Participants' selection

University undergraduates from non-biomedical studies (> 18 years) were invited to fill in the questionnaire. After the procedures were explained, the participants willing to participate were enrolled in the study, with no dropouts. These participants were selected because they present a higher literacy level than that of the majority of the Portuguese population, since only less than 75% of the Portuguese population completed the 9th grade (2011 census data),²⁸ and at the same time they are expected to lack specific health knowledge. In order to avoid biases, the following exclusion criteria were set: participants with possible specific health knowledge; non-native Portuguese speakers. The specific health knowledge was assessed inquiring if participants had prior 1) formal instruction in health, 2) experience in taking care of patients, 3) working experience in healthcare, or 4) any other situation that they considered might exceptionally have promoted their health knowledge. Overall, 26 participants were enrolled in this study (October 2012). The sample size of this study was based on the recommendations of the *European Guideline on the readability of the labelling and package leaflet*, i.e. enrolment of at least 20 participants.^{3,29}

2.3 Statistical analysis

Chi-square tests ($p < 0.05$; 95% confidence interval) were used to compare the proportion of correct/incorrect answers and the proportion of A&S in the PL of medicines from different: 1) therapeutic groups, 2) types of approval, 3) routes of administration, and 4) types of dispensing. SPSS (version 19) was used.

3. Results

In this section, the results of the descriptive and interpretation study are presented.

3.1 Descriptive study

A total of 828 different A&S (6407 occurrences) were identified in the 531 PL. The most prevalent groups of A&S were units of measures and chemical symbols (Table 1). 359 A&S (43.4% of 828) occurred only once (e.g. 2½). By contrast, 92 A&S (11.1% of 828) occurred more than 12 times (e.g. *mg*, *E171*). An average of 12.1 A&S (SD = 13.1) per PL was found. 38% PL contained more than 10 A&S (whether different or not). PL from anti-infective medicines (16 out of 45 PL) contained the highest proportion of A&S (more than 20 per PL), while the PL from dermatological medicines (34 out of 37 PL) contained the lowest proportion of A&S (less than 10 A&S per PL).

Table 1. Distribution of abbreviations and symbols

	A&S Groups	Number ^a	%	Occurrences	%
1	Units of measure	128	15.5	1521	23.7
2	Chemical symbols	211	25.5	985	15.4
3	Fractions or numbers in association with symbols or letters	68	8.2	501	7.8
4	Names of diseases	56	6.8	323	5.0
5	Micro-organisms	53	6.4	189	2.9
6	Drug names or therapeutic-related information	81	9.8	966	15.1
7	Administration	18	2.2	147	2.3
8	Information on anatomical and/or physiological issues	57	6.9	308	4.8
9	Enzymes	42	5.1	201	3.1
10	Mathematical or pharmacokinetic items	11	1.3	242	3.8
11	Marks on the surfaces of medicines	55	6.6	73	1.1
12	Common use	16	1.9	740	11.5
13	Other	32	3.9	211	3.3
	Total	828	100	6407	100

^a Number of different symbols and abbreviations in each group

The proportion of PL with more than 10 A&S in prescription-only medicines (41.1%, 174 of 423 PL) was statically greater than in OTC (23.1%, 25 of 108 PL) (Chi-Square = 13.4, $p=0.004$). Also, the proportion of PL with more than 10 A&S in medicines for parenteral administration (60.5%, 52 of 86 PL) was statistically greater than in oral preparations (37.3%, 116 of 311 PL), and other administration routes (23.1%, 31 of 134 PL) (Chi-Square = 35.9, $p<0.001$). The proportion of A&S in the PL of medicines approved via centralized vs. non-centralized procedure was not statically different. Overall, 1618 A&S (25.1% of 6407) were non-compliant with the legal requirements (e.g. abbreviations with full correspondence in a language other than Portuguese, or use of ">" or "<") (Table 2).^{3,9,23}

Table 2. Abbreviations and symbols non-compliant with the legal requirements

	Occurrences	%
Abbreviations with full correspondence in English	783	12.2
Fractions	294	4.6
> or <	265	4.1
Numerical dose and unit of measure run together	124	1.9
Abbreviation of active substances	74	1.2
μ	56	0.8
U	22	0.3
Other	4789	74.9
Total	6407	100

3.2 Exploratory interpretation study

Because in 1 of the questionnaires the description of the meanings of the A&S was not given, and 7 had more than one third of errors in the control questions, 8 of the 26 initial questionnaires were excluded. The participants were mainly females ($n=15$, 83.3%), with an average age of 20.5 ± 2.7 (Table 2). A total of 3462 test questions were

answered, but only 343 (9.9%) were considered correct. In the majority of the cases, the participants immediately assumed not to know the A&S, and the null answers were rare. A total of 202 control questions were answered and 156 (78%) were marked correct. The proportion of correct answers between the control and test questions was statistically significantly different (Chi-square = 549.7; $p < 0.001$). A&S from units of measure (45 A&S) were correctly answered in 19.5% (122 out of 624 answers), and only 8.1% of the remaining types of A&S (234 out of 2860 answers) were correct.

4. Discussion

The discussion is divided, as follows: general discussion, practical implications, and limitations.

4.1 General discussion

The results of the descriptive study show that A&S were widely used in the sampled PL, including A&S not compliant with the international regulation.^{13-15,22,23} Although these A&S are common in the glossaries of biomedical literature,^{19,22,23} their presence and/or their correspondent full meaning was infrequent in databases of common Portuguese.²⁷ In addition, the results from the interpretation study confirmed a very limited understanding on these A&S by the participants, even for a group of subjects with a level of education higher than the secondary school. In fact, only in very few cases A&S in the PL may be expected to be understood due to their widespread use (e.g. *HIV* or human immunodeficiency virus).

The PL with more A&S were those from the group of medicines for parenteral administration, prescription medicines and medicines highly used in Portugal (e.g. antibiotics), i.e. PL for which the readability is particularly important.³² The fact that some Portuguese PL are direct translations of PL from medicines available in other European countries,^{3,9,13-15,29,30} also strongly suggest the widespread use of A&S in PL in use in other European countries. A significant number of A&S was not compliant with the regulatory requirements.^{3,9,13-15,29,30} For instance, some A&S were not standardized in accordance to the requirements of the European Directorate for the Quality of Medicines^{30,31} (e.g. *IV*. instead of *i.v.* for intravenous, or the high proportion of abbreviations with correspondence in other languages than Portuguese). Knowing that patients often can not interpret technical A&S,^{11,33,34} the presence of this type of items may be especially problematic for countries, such as Portugal, where the average level of education is still quite low.³⁵ It is well known that the general population have difficulties in understanding PL information.^{36,37} The participants in this study were purposively selected from a higher literacy level. Despite their level of education, our subjects also showed great difficulty in understanding A&S. This type of items may thus pattern like other highly technical, specific and low frequent terms that tend to negatively impact on patients' comprehension^{11,36,37}, and this is not overridden by a rather high level of education.

Overall, the findings of the present study support a low readability of aspects of the sampled PL,^{14,16} a higher risk of misinterpretations, and consequently additional issues for patients' safety. Reducing the use of A&S in PL is required in order to improve readability, thus contributing to assure patients' comprehension of the information conveyed by unfamiliar A&S, such as some units of measure internationally accepted (e.g. *mmole*).²⁷ Additionally, software applications may be used, like PreText, to automatically screen A&S in PL in order to contributing to ensure their readability and regulatory compliance. It is expected that health professionals (e.g. physicians, pharmacists and nurses) will also benefit from a more appropriate and clear explanation of the technical A&S. The findings of this study may contribute to improve the readability and quality of Portuguese PL, with possible extensions to PL in use elsewhere in Europe, since some Portuguese PL are direct translations of PL found in other European countries.

4.2 Practical implications

Information design techniques should be developed in order to improve the intelligibility of PL, which should include the limitation in the use of A&S, together with other procedures, such as a systematic reduction of the use of jargon (technical and scientific terms) or the presence of a website where people may improve a certain PL. The use of A&S should be strictly supervised by the medicine agencies, and some marketed PL seem to require revision.

Automatic methods for translations involving text mining and the detection of improper use of A&S or jargon may be useful in the present or new PL.

4.3 Limitations

Contrary to the legal recommendations, patients were not enrolled in the comprehension study.³ The A&S were isolated tested in the interpretation study and not inserted in the original PL text, and this means that the study is not entirely ecological in the sense that it does not reproduce the exact conditions of PL potential users. The number of participants may be considered rather low. The participants were asked to provide a brief explanation of the meaning of the A&S in the final column, and this may have dissuaded responders from admitting that they knew a particular A&S.

5. Conclusion

A substantial number of A&S non-compliant with the legal requirements were identified in the sampled PL. Moreover, it was found that a substantial number of A&S was not understood by a group of people with a rather high level of education. It seems therefore advisable to reduce and optimize this type of items in PL. Software applications may be useful in the development and validation of PL before the medicine reaches the market. Health authorities should supervise more strictly the occurrence of A&S with negative impact in PL readability.

Acknowledgements

FCT (Fundação para a Ciência e Tecnologia; Grant: SFRH/BD/76531/2011). The second and third authors would also like to acknowledge financial support by PEst-OE/LIN/UI0214/2013, FCT, Portugal.

Disclosure

A brief Letter on this issue *Using an automatic tool to identify potential readability issues in a large sample of medicinal package inserts* was accepted in *Methods of Information in Medicine*, although presenting different data.

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